REMARKS

I. Objections to the Disclosure

The Examiner first objects to the Oath/Declaration as not being in permanent ink, or its equivalent in quality. Attached please find a substitute declaration which meets the requirements of 37 CFR 1.52(a).

The Examiner next objects to the drawings as not being in permanent ink. Accordingly, August 7, 2001 Applicants' filed substitute drawings to alleviate this objection.

Next, the Examiner has objected to the disclosure as containing an embedded hyperlink. This hyperlink has now been deleted, thereby rendering this objection moot.

Finally, claims 13-17 have been amended to depend from claim 12 instead of claim 1, thereby alleviating the Examiner's objection in this regard.

II. Claim Rejections - 35 U.S.C. § 112, First Paragraph

Claims 22-23 were rejected under 35 U.S.C. § 112, first paragraph, for lack of enablement. These claims have now been canceled, thereby rendering this ground of rejection moot.

III. Claim Rejections – 35 U.S.C. § 112, Second Paragraph

Claim 20 was rejected under 35 U.S.C. § 112, second paragraph, as being indefinite. Applicants have now substituted "which hybridizes" for "capable of hybridizing" in accordance with the Examiner's suggestion in order to alleviate this ground of rejection. Applicants thank the Examiner for this suggestion.

IV. Claim Rejections - 35 U.S.C. § 103

Claims 1-7, 10-12, 18, 19, 21-24, and 25 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Kool (U.S. Patent No. 5,714,320) and in view of Bertioli (PCR Cloning Protocols, vol. 67, 233-238, 1997). Applicants respectfully traverse this rejection.

The PTO bears the burden of establishing a case of prima facie obviousness. In re Fine, 837 F.2d 1071, 1074 (Fed. Cir. 1988). It is axiomatic that in order to establish a prima facie case of obviousness, it is necessary for the examiner to present evidence, preferably in the form of

some teaching, suggestion, incentive or inference in the applied prior art, that one having ordinary skill in the art would have been led to combine the relevant teachings of the applied references in the proposed manner to arrive at the claimed invention. See e.g. Carella v. Starlight Archery, 804 F.2d 135 (Fed. Cir. 1986); Ashland Oil, Inc. v. Delta Resins & Refractories, Inc., 776 F.2d 281 (Fed. Cir. 1985). This suggestion cannot stem from the applicant's own disclosure, however. In re Ehrreich, 590 F.2d 902 (CCPA 1979).

Although the suggestion to combine references may flow from the nature of the problem, "[d]efining the problem in terms of its solution reveals improper hindsight in the selection of the prior art relevant to obviousness." Monarch Knitting Machine Corp. v. Sulzer Morat Gmbh, 139 F.3d 877, 880 45 USPQ2d 1977, 1981 (Fed. Cir. 1998). Federal Circuit case law makes clear that the best defense against hindsight-based obviousness analysis is "the rigorous application of the requirement for a showing of a teaching or motivation to combine the prior art references." Ecolochem, 56 USPQ2d at 1073. (Emphasis supplied).

The Examiner's obviousness rejection is based on the premise that it would have been obvious to have modified the teachings of Kool directed to a rolling circle method for amplifying single-stranded oligonucleotide in the manner taught and claimed by Applicants. Although the Examiner admits that Kool is silent with respect to any to teaching of primer extension or amplification of 3' and 5' ends of nucleic acid molecule or cDNA, the Examiner argues that the disclosure of Bertioli renders this teaching obvious. For the following reasons, however, the Examiner has failed to establish a prima facie case of obviousness.

The Examiner states it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the single-strand circular oligonucleotide/or polynucleotide amplification method as taught by Kool with the RACE method to achieve the expected advantage of amplification of 3' and 5' ends of a cDNA and cloning full-length cDNA. The Examiner argues that the motivation for this would have been an approach to amplify both the ends of cDNA in a single reaction vessel.

The first problem with the Examiner's argument, however, is that there is no incentive to combine the Kool and Bertioli references. The Examiner argues that the motivation to combine the references "would have been an approach to amplify both the ends of cDNA in a single reaction vessel." (Office Action, p. 5). However, as acknowledged by the Examiner, there is no

teaching or suggestion whatsoever in Kool to amplify the 3' and 5' ends of cDNA. Thus, without the benefit of hindsight, a person skilled in the relevant art would not have looked to the teachings of the Kool reference in order to improve or modify the RACE amplification method disclosed by Bertioli.

The Examiner's obviousness rejection further fails since, even if in combination, the Kool and Bertioli references do not teach the advantages of the amplification method of the claimed invention. Bertioli teaches a method of rapid amplification of the cDNA ends (RACE) which allows the amplification of either the 5' or 3' end of a specific cDNA starting from mRNA population. As explained in the specification on page 5, the RACE method uses one specific primer coupled with a non-specific primer. Thus, because the non-specific primer could interact with any mRNA, this method tends to generate numerous false positives resulting in decreased efficiency. (Spec. p. 5). This is in contrast to Applicants' claimed method of introducing first and second sequence specific primers to a circular polynucleotide sample, and initiating a primer extension amplification reaction. (See independent claims 1, 12, 18, 24, 25, and new claims 26 and 27. Neither Kool nor Bertioli teach the use of sequence specific primers in amplifying the 5' or 3' end of a nucleic acid sequence. It is therefore respectfully submitted that claims 1, 12, 18, 24-27, and depending claims 2-7, 10-11, and 19 are not rendered obvious by Kool in view of Bertioli.

Applicants has also added new claims 26 and 27 which are directed to the subject matter of claim 1 along with the provisions of claims 8 and 9, respectively. As claims 8 and 9 were not the subject of the Examiner's obviousness rejection, it is respectfully submitted that claims 26 and 27 are also not obvious. Likewise, claim 20 was also not rejected on grounds of obviousness, and should also be allowable.

V. Conclusion

It is believed the application is in a prima facie condition for allowance. Allowance is respectfully requested.

Enclosed please find a check for $84 for the addition of two new independent claims. Please consider this a request for any extension inadvertently omitted, and charge any additional fees to Deposit Account No. 26-0084.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned "**Version with markings to show changes made.**"

Respectfully submitted,

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AMENDMENT — VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the Specification

Paragraph beginning at line 10 of p. 10 has been amended as follows:

Once the circular nucleic acid is formed, then a template extension amplification reaction is carried out with gene specific primers. The design of the first and second primers differs from that of traditional PCR of cDNA first in that using a single nucleic acid strand as template. The primers are instead designed so that each one has a 3' end of the primer which is toward either the 5' or 3' end of the polynucleotide. This means that the forward primer will typically be towards the 3' end of the molecule and the reverse primer will be towards the 5' end of the molecule. For example, if a known sequence comprises 5'-ATATATATGCGCGCGC-3' a forward primer would be 5'-CGCGCGCG-3' to hybridize with the 3' end of the molecule and the second or reverse primer would be 5'-ATATATAT-3' to hybridize with the 5' end of the molecule and having its 3' end towards the 5' of the target gene. See Figure 1. Design of primers for amplification and extension reactions are commonly known in the art of PCR amplification and the remainder of primer design is standard. A brief summary of oligonucleotide primer design is disclosed herein. In addition a discussion of primer design can be located in "Molecular biology Techniques Manual" third edition CRC Press, Editors, Coyne et al.[available at www.uct.ac.za/microbiology/pcroptim.htm.] In addition, there are a number of publically and commercially available computer programs to aid in design of primers including, BLAST, PrimerGen, Primer (Stanford), Amplify, Primer Design 1.04, PC-Rare, CODEHOP, Primer 3, and Net Primer (Premier (Premier Biosoft Int'l).

In the Claims

Claims 22 and 23 have been canceled.

Claims 12-13 and 20-23 were amended as follows:

12. (Amended)

A method for amplifying a nucleic acid molecule including the 5' and 3' ends comprising:

circularizing said nucleic acid molecule;

contacting said nucleic acid with first and second sequence specific primers; and

introducing a polymerase and a supply of nucleotide bases to said circularized nucleic acid molecule so that an amplification reaction occurs; wherein said region of said nucleic acid molecule outside of said first and second primers including the 3' and 5' ends of said molecule is amplified.

13. (Amended)

The method of claim [1] 12 wherein said ligase is T4 DNA ligase.

20. (Amended)

A method of nucleotide primers for use in PCR amplification of circularized cDNA comprising:

a forward primer of from about 4 to about 35 contiguous bases [capable of hybridizing] which hybridizes to a gene which is to be amplified, and

a reverse primer of from about 4 to about 35 contiguous bases [capable of hybridizing] which hybridizes to a gene which is to be amplified, wherein said forward primer is towards the 3' end of said gene and said reverse primer is towards the 5' end of said gene.

21. (Amended)

A kit for amplifying first strand cDNA from a sample of mRNA comprising:

a DNA ligase,

a DNA polymerase,

a reverse transcriptase without Rnase H activity;

an enzyme for degrading mRNA from a cDNA - mRNA hybrid;

each of the four deoxynucleoside triphosphates (dATP, dCTP, dGTP, and dTTP); and

sequence specific primers.

Claims 26-27 were added:

26. (New)

A method for amplifying a polynucleotide sequence comprising:

obtaining a linear, single strand polynucleotide sample;

ligating the ends of said sample to form a circular shaped sample;

introducing first and second sequence specific primers to said circular sample, wherein said primers are degenerate primers; and

initiating a primer extension amplification reaction to increase copy number of said circular sample.

27. (New)

A method for amplifying a polynucleotide sequence comprising:

obtaining a linear, single strand polynucleotide sample;

ligating the ends of said sample to form a circular shaped sample;

introducing first and second sequence specific primers to said circular sample, wherein said first and second primers are designed to hybridize to from about 4 to about 35 contiguous bases from a sequence known or suspected to be present in said nucleic acid sample; and

initiating a primer extension amplification reaction to increase copy number of said circular sample.